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SUCCESSFUL USE OF LONG-ACTING OCTREOTIDE FOR INTRACTABLE CHRONIC GASTROINTESTINAL BLEEDING IN CHILDREN

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Abbreviations: Gastrointestinal bleeding (GIB), long-acting octreotide (OCT-LAR), Oesophago-gastroduodenoscopy (OGD), gastroenteropancreatic tumors (GEP tumors) barium meal and follow-through (BMFT), abdominal contrast-enhanced computed tomography (CT) scan, wireless capsule endoscopy (WCE), abdominal magnetic resonance imaging (MRI), Kasai portoenterostomy (KPE)

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The use of the drug was approved by our institution for each individual patient.

Key words: gastrointestinal bleeding, portal hypertension, octreotide, long-acting octreotide, depot octreotide, children

ABSTRACT (Word count: 259)

Background and Aims: Octreotide reduces splanchnic blood flow and is effective in gastrointestinal bleeding (GIB) due to portal hypertension. Monthly long-acting octreotide (OCT-LAR) with an efficacy and safety profile similar to subcutaneous daily administration, presents an attractive option for long-term therapy. We report our experience with OCT-LAR for severe/recurrent GIB in children with portal hypertension secondary to chronic liver disease or portal vein thrombosis who were unresponsive to standard interventions.

Patients and Methods: 9 patients, 7 males, who received OCT-LAR between 2000 and 2009 were studied retrospectively (median age at first bleeding 21 months; range, 1 month-14.5 yrs). The dose (2.5 to 20 mg intramuscularly monthly) was extrapolated from that used in adult acromegaly and neuroendocrine tumours (10-60 mg/month). Response to treatment was assessed by comparing number of bleeding events, hospital admissions for acute bleeding and number of blood units required during the year before and year after starting OCT-LAR.

Results: OCT-LAR led to a reduction in the number of bleeding episodes in all children, and to cessation of bleeding in 7. Two children listed for transplantation because of severe GIB were removed from the list. No serious side effects immediately attributable to OCT-LAR were observed. One child developed growth hormone deficiency and hypothyroidism during a prolonged period of treatment with subcutaneous octreotide before commencing OCT-LAR.

Conclusion: OCT-LAR can control severe intractable recurrent GIB in children with portal hypertension. Prospective randomized controlled trials and pharmacokinetic studies are indicated to establish the optimum dose and length of treatment of OCT-LAR and to confirm its efficacy and long-term safety in children.

INTRODUCTION

Portal hypertension and gastrointestinal bleeding (GIB) are major complications of chronic liver disease [1]. Oesophago-gastroduodenoscopy (OGD) and/or ileocolonoscopy can identify the source of bleeding in up to 95% of patients, allowing targeted treatment. [2]. When the source of bleeding is not obvious, presumably in the small bowel, the treatment options are limited. Consequences of persistent or recurrent bleeding in paediatric age include fatigue, poor school attendance/performance and depression, secondary to chronic anaemia. Intractable bleeding necessitates multiple investigations, surgical interventions and even consideration for liver transplantation [3]. The associated mortality ranges from 2.5%-20% [4]. Treatment options for occult bleeding are limited, giving relevance to empirical pharmacological approaches [2,5-11].

Octreotide, the first somatostatin analogue introduced for clinical use, inhibits the release of growth hormone, glucagon, and insulin. Octreotide markedly reduces splanchnic blood flow and has a half-life 30-100-fold longer than somatostatin [12,13]. It has a high affinity only to somatostatin receptors subtype 2 (sst2) and subtype 5 [14]. sst2 is largely expressed in neuroendocrine and non-neuroendocrine cells of the human gastrointestinal tissue [15]. Octreotide is licensed for symptomatic control and reduction of growth hormone and somatomedin C plasma levels in patients with acromegaly and for the relief of symptoms associated with functional gastroenteropancreatic tumors (GEP tumors) in adult patients [12]. In children, octreotide has been used on an unlicensed basis for treatment of hyperinsulinaemia, secretory diarrhoea, pancreatitis, chylothorax and acute GIB either as a continuous infusion or three times daily subcutaneous injection [16-19]. The long acting (OCT-LAR) formulation of octreotide can be administered once a month with similar efficacy and safety profile to subcutaneous daily administration [20,21,22]. Following a single intramuscular injection, OCT-LAR concentrations reach a plateau at day 14 and remain relatively constant for the following 3-4 weeks in adults [23]. OCT-LAR therefore represents an attractive option for long-term therapy of GIB. Use of OCT-LAR in children is limited by lack of pharmacokinetic data, clinical experience, and several described adverse events,

including nausea, abdominal cramps, diarrhoea, fat malabsorption, reduced glucose tolerance and development of gallstones [20-24]. Moreover, octreotide has the potential to interfere with endocrine mechanisms, a side effect particularly significant in the paediatric population. We report our experience on the use of OCT-LAR in treating severe GIB in children with portal hypertension secondary to chronic liver disease or portal vein thrombosis not responding to multiple conventional interventions, including variceal sclerotherapy or banding and intravenous or subcutaneous octreotide.

PATIENTS AND METHODS

The Paediatric Liver Service at King's College Hospital, London, UK is a tertiary referral centre where some 500 new children with acute or chronic liver disorders are referred each year. From our database we have identified and reviewed retrospectively the clinical and laboratory data of all children in whom OCT-LAR, commercially available since 1998, has been used. Indications for OCT-LAR therapy were persistent GIB of unknown origin or resistant variceal bleeding previously treated with banding or sclerotherapy, with no or only partial response to intravenous octreotide.

Obscure GIB was defined as bleeding in the absence of an obvious cause; occult GIB as laboratory evidence of blood in the stools without macroscopic change in their appearance [10]. Cause of bleeding were investigated using a combination of tests, as detailed in the result section.

In the patients in whom oesophageal and/or gastric varices were identified, banding or sclerotherapy were performed. All patients with acute haemorrhage unresolved by sclerotherapy and banding were treated with a standard continuous intravenous octreotide infusion (50 mcg per hour, irrespective of the weight), slowly weaned down over 24-48 hrs after bleeding stopped [11]. If persistent re-bleeding occurred after at least 4 sclerotherapy/banding sessions, necessitating frequent hospital admissions and numerous transfusions, the children were considered for treatment with OCT-LAR.

OCT-LAR was administered intramuscularly at a dose of 2.5 to 20 mg monthly. The initial dose was extrapolated from adult data for the treatment of acromegaly and neuroendocrine tumours, i.e. 20-60 mg every 4 weeks [25][26] . The paediatric dose was calculated as percentage of an average adult weight rounded to the closest 2.5 mg for ease of administration (not exceeding 20 mg). Blood transfusion was given when haemoglobin values fell below 8 g/dl or when acute clinical bleeding occurred (1 transfusion unit = 250 ml blood). Response to treatment was assessed using the number of bleeding events, hospital admissions for acute bleeding episodes and the number of blood units required during the year before and the year after initiation of therapy. Adverse effects during therapy were recorded retrospectively from the clinical notes.

STATISTICAL METHODS

The primary end point was to determine the number of recurrent bleeding episodes in the 12 months after treatment with OCT-LAR compared to the previous 12 months. Secondary end points included the effect of OCT- LAR on the number of blood units transfused, on the number of hospital admissions and on the length of hospital stay. Continuous variables are described by means of median values and ranges. Wilcoxon signed rank test was used to compare the number of bleeding events, number of transfusions, number of hospital admissions and number of days in hospital 1 year before and 1 year after OCT-LAR therapy. A *P* value <0.05 was considered significant.

RESULTS

Nine patients, 7 males, who had received OCT-LAR from 2000-2009 were identified and studied. The median age at first bleeding was 21 months (range, 1 month-14.5 yrs). Their diagnoses, treatment and outcome are summarized in Table 1. All patients had a history of intermittent acute GIB (haematemesis, melaena, haematochezia), leading to severe

anaemia requiring repeated blood transfusions. The underlying disease was biliary atresia in 7 (78%) children, 4 (57%) of whom had a successful (e.g. leading to normalization of serum bilirubin) Kasai portoenterostomy (KPE), while the remaining 3 (43%) with persistent jaundice eventually required liver transplantation. Two of them developed portal hypertension as a consequence of portal vein thrombosis after liver transplant.

One child had Klippel-Trénaunay-Weber syndrome and thrombosis of the portal vein, while another had diffuse gastrointestinal arterio-venous malformation complicated by arterialisation of the portal vein system and subsequently required partial hepatectomy.

All patients had portal hypertension characterised by recurrent bleeding and thrombocytopenia with 7 patients reported to have splenomegaly. The remaining two, patients 5 and 8 with no splenomegaly had polysplenia as part of their biliary atresia-splenic malformation (BASM) syndrome. The universal presenting features were chronic anaemia (9 patients, 100%) and melaena (9 patients, 100%), while haematochezia was present in 7 (78%) and haematemesis in 6 (67%) children. There was no personal or family history of haemorrhagic disorders. Patient 4 was on long-term warfarin therapy due to the underlying Klippel-Trénaunay-Weber syndrome and chronic disseminated intravascular coagulopathy [27-29]; patient 8 was temporarily treated with aspirin (8 mg/kg) due to a thrombus in the inferior vena cava and transiently high platelet count. After 3-month treatment aspirin therapy was discontinued due to anaemia, faecal occult blood, and thrombocytopenia which continued following the withdrawal. Three patients (patients 6, 7 and 9) were on maintenance propranolol therapy (0.5-1 mg/Kg/day) both before and after treatment with OCT-LAR.

The tests performed to investigate the cause of bleeding included: oesophagous gastro duodenoscopy (OGD) in 9 (100%) patients, colonoscopy in 6 (67%), video capsule endoscopy in 4 (44%), angiography in 5 (56%), explorative laparotomy in 5 (56%), technetium-99m-labelled erythrocytes scintigraphy in 2 (22%), abdominal computerised

tomography (CT) scan in 2 (22%), abdominal magnetic resonance imaging (MRI) in 2 (22%), and barium meal and follow through in 1 (11%).

A bleeding site was found in 5 cases (56%) (Table 1). Patient 1 had a vascular lesion, bleeding profusely, above the recto-sigmoid junction. This was detected by colonoscopy and treated by electro-coagulation. Grade 3 oesophageal varices and grade 2 gastric varices were detected by OGD in patient 4 and the oesophageal varices were subsequently banded. Teleangiectasiae were also found by colonoscopy in the low caecum in this patient, but could not be treated. In patient 5 multiple bleeding lesions in the Roux-loop with fresh blood and clots were detected during laparotomy, and in patient 6 multiple friable haemorrhagic polypoid lesions were found in the proximal part of duodenum which could not be treated. In patient 8 grade 3 oesophageal varices were detected by OGD and treated with sclerotherapy. In all cases where the bleeding sites were treated, rebleeding occurred after the procedures with no reduction in the rate of episodes and blood transfusion requirements. In the remaining 4 children (44%) no active bleeding site was found, though non-bleeding oesophageal varices were seen in patient 2 during OGD and CT scans suggested presence of Roux loop varices in patients 3, 7 and 9.

The median age at commencement of therapy with OCT LAR was 71 months (range, 3-190). The median number of injections received was 13 (range, 1-90). Three patients received only one dose. The median dose was 0.36 mg/kg (range, 0.16-0.95). The patients have been followed up for a median of 62 months (range, 12-111) from initiation of the therapy (Table 1).

Three patients were excluded from statistical analysis: Patient 1 because he had received subcutaneous octreotide immediately prior to starting OCT-LAR, patient 5 as he was only 3 months old at initiation of therapy and patient 8 because his follow-up was shorter than 12 months. Patient 8 had received a single dose of OCT-LAR with no further bleeding, but underwent transplantation after 4 weeks. In the remaining 6 patients the median number of injection was 12.5 (range, 1-36), the median dose received for these 6

patients was 0.38mg/kg (range, 0.29-0.95), and the median follow up was 65.5 months (range, 5-100) from the initiation of treatment. In these 6 patients all parameters were analysed for the year before and the year after the initiation of therapy. The overall number of bleeding events decreased in all children after OCT-LAR therapy (Table 2) Two patients (Patients 3 and 6) stopped bleeding immediately after the first dose of OCT-LAR. However, Patient 3, whose OCT-LAR treatment was discontinued after 10 months, had a single bleed 7 months later. Patient 6 who had no reported bleeding episodes for 18 months after the first dose of OCT-LAR, started bleeding again, though the severity and frequency of the bleeding episodes were markedly reduced when compared to before receiving OCT-LAR. Patient 2 had a single dose of OCT-LAR with a conspicuous reduction in bleeding episodes and no further OCT-LAR was administered. The remaining 3 patients (Patients 4, 7 and 9) stopped bleeding after 3, 7, and 2 injections (Table 1). The median number of blood transfusion units required per patient as well as the number of hospital admissions decreased in all children (Table 2). A reduction in the median length of hospital stay was also observed (Table 2). Five out of eight patients received monthly OCT-LAR injections for >6 months.

Excluding Patient 1, who had already stopped bleeding while on subcutaneous octreotide prior to commencement of OCT-LAR, bleeding ceased in 7 of the remaining 8 patients: in 4 after the first injection of OCT-LAR (two of whom received only one dose) and in 3 after a median of 3 doses (range, 2-7) (Table 1).

OCT-LAR was well tolerated in all patients. There were no reports of tachyphylactic reactions, gallstones and liver or pancreatic disturbance (25). Apart from patient 1 (see below), no endocrine abnormalities were noted.

Patient 1 received subcutaneous octreotide (9.7 mg/kg/day in three divided doses) for 11 months before starting OCT-LA. As this was our first use of prophylactic subcutaneous octreotide, the dose was derived from the hyperinsulinaemia treatment (up to 40 mcg/kg/day). Episodes of bleeding reduced from 219 over 12 months prior to sub

cutaneous octreotide to 14 in the first seven months of subcutaneous therapy. Subsequently the bleeding stopped. OCT-LAR was started 11 months after subcutaneous octreotide therapy commenced and continues to the present day. Bleeding has never resumed and after 3 years the frequency of OCT-LAR was reduced to every six weeks. The family remains reluctant to stop therapy due to their concerns that GIB may re-occur. Whilst on subcutaneous octreotide, Patient 1 developed diarrhoea and abdominal bloating, which resolved soon after initiation of OCT-LAR. He was also diagnosed with growth hormone deficiency during the first year he was receiving daily subcutaneous octreotide therapy. At the age of 14 years, whilst on subcutaneous octreotide, a growth hormone release hormone test showed no growth hormone response, and his height velocity had reduced markedly from 8.2 cm/year to 3.1 cm/year. Testicular volumes were appropriate for the pubertal growth spurt. Due to the reduced height velocity, the decision was made to commence somatropin therapy for the remaining growth years. Fourteen months after starting subcutaneous octreotide serum T4 level was at the lower limit of normal at 10.1 pmol/L (normal range, 10-23 pmol/L), leading to the initiation of levothyroxine supplements (100 mcg/day). The patient's growth and development has subsequently been normal (along the 50th centile for height and 75th for weight throughout his adolescence).

At last follow up, 7 patients were alive with no evidence of GIB: 3 on regular OCT-LAR treatment (Patient 1, 7 and 9), 1 on intermittent (before long haul flights) treatment (Patients 3), 2 off treatment (Patient 2, re-transplanted for chronic rejection 6 years after the first transplant and Patient 4). Patient 6 has minor GIB episodes triggered by sharp food treated with OCT-LAR (about 3 injections/year). One patient had a liver transplant performed 4 weeks after starting OCT-LAR (Patient 8). Two patients (Patients 7 and 9), who had been listed for re-transplant and transplant, respectively, because of severe persistent GIB, were removed from the transplant list, as they stopped bleeding on OCT-LAR. One patient (Patient 5) died of an intracranial haemorrhage of unknown 14 months after a single dose of OCT-LAR.

DISCUSSION

Our data provide novel evidence that OCT-LAR is effective, with no apparent serious adverse effects, in controlling severe GIB in children with advanced portal hypertension, in whom conventional endoscopic and medical treatments fail. Present international guidelines also include transjugular intrahepatic portosystemic shunting (TIPS) as a potential management option with considerable technical limitations in infants and small children [30], but in our centre TIPS is considered only as a bridge to liver transplantation.

Continuous intravenous infusion of somatostatin analogues remains a standard therapy for acute GIB episodes in both adult and paediatric patients with portal hypertension [11,15-19]. Subcutaneous octreotide therapy is effective in preventing recurrent bleeding episodes in adults [31-34], but the requirement for three times daily administration renders it impractical for long term prophylaxis, particularly in children. Moreover, fluctuating octreotide serum levels have been reported with subcutaneous therapy [33]. In adults, OCT-LAR administered on a monthly basis has similar efficacy to subcutaneous therapy, and results in sustained blood levels [21,32,33]. These features of OCT-LAR prompted us to use it in children with refractory GI bleeding, despite the lack of paediatric studies for this indication.

In paediatrics, OCT-LAR has been used anecdotally for the treatment of Prader-Willi syndrome, but with no firm dose recommendations [24]. The dose we used was extrapolated down for weight from that recommended for the treatment of acromegaly and neuroendocrine tumours in adults [median dose 0.36mg/kg/month (range 0.16-0.95mg/kg/month)], corresponding to an adult dose of 23mg/month (range 10-60mg/month) [12,26]. One child received a dose of 20mg, 0.95mg/kg/month equivalent to 60mg in an adult patient. This high dose, similar to that employed in some patients with neuroendocrine tumours [26], was chosen due to the severity of his symptoms at the time of treatment

initiation. The dose was not proportionally increased throughout his childhood as his symptoms remained well controlled; his current dose of 20mg is equivalent to 0.6mg/kg.

It is possible that OCT LAR doses lower than those used might have been equally effective, as in few adults in whom OCT-LAR has been employed for gastrointestinal bleeding [35-38], both 20 mg and 10 mg monthly doses were reported to be effective [35-38]. A randomized controlled study of eighteen adult cirrhotic patients with portal hypertension showed a decrease of the hepatic venous pressure gradient (HVPG) in the treated arm, but not in the placebo arm using OCT-LAR at a dose of 20 mg monthly for a 3 month period [34]. Though a similar proportion of treated and untreated patients (70% and 62% of octreotide and placebo treated patients, respectively) were taking β -blockers, it is possible that combined treatment with OCT-LAR and propranolol may have had an influence on the HVPG. In our study only 3 patients were taking propranolol at low doses during the year before and the year after starting OCT-LAR. As we did not measure HVPG we cannot comment on the possible cumulative effect of the β -blocker. In another study, on the assumption that the effect of octreotide on the GI tract - mediated by ss2A receptor subtypes – may be achieved by doses lower than those required to inhibit tumour growth, Scaglione et al. assessed the effectiveness of 10 mg/month OCT-LAR in controlling chronic bleeding from gastrointestinal angiodysplasias in 13 adult patients [37]. During treatment a decrease in the number of transfusions as well as in the number and length of hospital admissions was noted; in three patients who did not respond to 10 mg/month the dose was increased to 20 mg/month with no benefit.

The present study shows a significant reduction in the number of bleeding episodes in the year following the start of OCT-LAR treatment in all children, and, in addition, it shows complete cessation of bleeding in seven of them. Most importantly, two children who were listed for liver transplantation because of the severity of their GIB were removed from the list and remain well with no further episodes of bleeding several months after starting OCT-LAR treatment.

As our study was not randomized and there was a great variation in the frequency and number of injections received by our patients, it is difficult to draw conclusions on how many doses are required to control bleeding. Among the eight patients who stopped bleeding, four did so after the first injection of OCT-LAR, two of whom received only one dose (one died and one was transplanted); one patient had already stopped bleeding on subcutaneous octreotide therapy prior to commencement of OCT-LAR; the remaining three stopped bleeding after a median of 3 (range, 2-7) injections. For Patient 2, who had a marked reduction of bleeding episodes after a single dose, the role of OCT-LAR remains speculative. We did not observe serious side effects immediately attributable to OCT-LAR treatment. Patient 5 died 11 months after a single dose of OCT-LAR, but, given the time interval between receiving OCT-LAR and death of intracranial haemorrhage, it is unlikely that the use of octreotide has contributed to his death. Patient 1 developed growth hormone deficiency and hypothyroidism during a prolonged period of treatment with a relatively high dose of subcutaneous octreotide (10 mcg/kg/day compared to 0.16 mcg/kg monthly whilst receiving OCT-LAR) before starting OCT-LAR. As no further bleeding episodes occurred in the following 8 years of OCT-LAR therapy, it is possible that, had OCT-LAR been used initially, he would have stopped bleeding without developing adverse effects, as we observed in the remaining 8 patients.

In contrast with the lack of side effects attributable to OCT-LAR in our series, a recent paper aiming at investigating the safety and efficacy of OCT-LAR in adult patients with Child Pugh Class A or B cirrhosis, no history of GI bleeding and small oesophageal varices, reports adverse events characterized by abdominal cramps, diarrhoea and hypoglycaemia in four out of ten patients treated with a dose of 30mg/month, while no serious side effects were detected in patients treated with 10mg/month.[39] In the same multicentre study no haemodynamic benefit with either OCT-LAR dose was demonstrated by measuring HVPg, but the authors emphasise that the quality of the HVPg tracings across centres was variable making interpretation difficult. Though both the end-points and the patient characteristics in that study are different from those in our report, it is intriguing

TABLE 1. PATIENT CHARACTERISTICS, DOSAGE OF LONG-ACTING OCTREOTIDE AND OUTCOME
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that no abdominal adverse effects or hypoglycaemia were reported in any of our children. It is important to note, however, that only three of our nine patients received an equivalent OCT-LAR dose $\geq 30\text{mg/month}$ if extrapolated. We suggest, therefore, that caution should be exercised before using doses at the higher end of the spectrum.

Due to its small size and its retrospective nature, this study is unable to recommend an optimal length of OCT-LAR treatment *vis a vis* the recurrence of bleeding and the risk of side effects, but an empirical approach with monitoring of the thyroid function and growth velocity appears to be prudent.

In conclusion, this pilot experience indicates that OCT-LAR may be effective in controlling severe recurrent GIB not amenable to conventional endoscopic treatment in children with portal hypertension caused by chronic liver disease and gastrointestinal vascular malformations. This therapy is less invasive than daily subcutaneous octreotide injections, reducing compliance issues. Adverse effects are uncommon but regular endocrine assessment, particularly in adolescent patients, is recommended. Pharmacokinetic studies and prospective randomized controlled trials are necessary in order to establish the optimum dose and length of treatment of OCT-LAR and to confirm its efficacy and long term safety in treating severe GIB in children.

Table 1

Pt No. (Sex)	Diagnosis	Age at first bleeding (months)	Source of bleeding	Age at first dose (months)	Dose (mg)	Dose (mg/kg)	No of doses	Follow up post therapy (No. of months)	Clinical details and outcome
1 (M)	BA successful Kasai	2.5	Throughout the gut	180	10	0.16	90	111	Subcutaneous octreotide for 11 months before OCT-LAR. Monthly OCT-LAR for 3 years, then 6-weekly to date. No further GIB. Growth hormone deficiency, hypothyroidism.
2 (M)	BA, failed Kasai PVT post-LT	12	Oesophageal varices	29	5	0.36	1	80	LT at 10 months of age. PVT 18 months post LT. Marked reduction of bleeding episodes after a single dose of OCT-LAR. PTLT then chronic rejection. Re LT at 7 years of age
3 (M)	BA successful Kasai	21	Roux loop varices	35	5	0.35	15	69	No GIB during a 10-month course of monthly OCT-LAR. GIB 7 months after stopping OCT-LAR, following a long haul flight. No further GIB with OCT-LAR administered 14 days before long haul flights (>5 hours)
4 (F)	KTW syndrome PVT	175	Grade 3 oesophageal varices grade 2 gastric varices, Telangiectasia in the lower caecum	190	20	0.29	15	62	Long-term Warfarin treatment. PVT diagnosed at 14 years. Severe GIB aged 14-16 years. Only one GIB episode during 15 doses of monthly OCT-LAR. One episode 2 months after cessation of therapy. No further GIB
5 (M)	BA failed Kasai	1	Roux loop	3	2.5	0.46	1	14	Died of intracranial haemorrhage aged 17 months, no further GIB. Post mortem refused by family.
6 (M)	Liver + gut AVM Portal vein arterialization	60	Oesophageal, gastric and duodenal varices	138	20	0.95	36	100	Microcephaly + developmental delay. Partial hepatectomy aged 3 years; banding of oesophageal varices aged 10 years. Propranolol 1mg/kg/day Monthly OCT-LAR from 11-17 years. No GIB after the first dose for 18 months and then a marked reduction in the number and severity of episodes. From age 17, minor GIB episodes triggered by sharp food treated with OCT-LAR about 3 times/year.
7 (F)	BA, failed Kasai PVT post-LT	23	Roux loop varices	124	20	0.47	13	12	LT at 1 year of age. PVT 1 year post LT. Unsuccessful porto-systemic shunt at age 9 years. Patient was prescribed propranolol 0.5mg/kg/day Re-listed for LT and started on 4-weekly OCT-LAR. Reduced GIB episodes for 6 months, then GIB stopped. Removed from LT list.
8 (M)	BA failed Kasai	11	Oesophageal varices	12	2.5	0.33	1	31	LT 4 weeks after OCT-LAR administration with no further GIB before surgery
9 (M)	BA successful Kasai	23	Roux loop	71	10	0.4	13	12	OCT-LAR started after 6-months severe melaena prompting listing for LT. Propranolol 0.5mg/kg/day No further GIB after the second dose and with monthly OCT-LAR injections to date. Removed from LT list.
BA: biliary atresia; PVT: portal vein thrombosis; LT: liver transplant; AVM: arterio-venous malformation; KTW: Klippel-Trenaunay-Weber; GIB: gastrointestinal bleeding									

Table 2

TABLE 2.
EFFECTS OF LONG-ACTING OCTREOTIDE TREATMENT ON BLEEDING EPISODES IN 6 PATIENTS (Patients 2, 3, 4, 6, 7, 9)

	Before therapy	After therapy	<i>P</i>
Observation period (months)	12	12	
Number of GIB events	22 (12-110)	1.5 (0-27)	<i>0.03</i>
Hospital admissions for GIB	5.5 (2-7)	0.5 (0-2)	<i>0.03</i>
Length of hospital stay (days)	47.5 (11-92)	2 (0-42)	<i>0.03</i>
Required blood units	5 (2-33)	0.5 (0-17)	<i>0.03</i>

GIB: gastrointestinal bleeding; Data are reported as median (range); Wilcoxon matched pairs test: $P < 0.05$ is statistically significant.

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